CHAPTER 8
SUMMARY, GENERAL DISCUSSION AND FUTURE DIRECTIVES
PREVIOUS CHAPTERS

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INTRODUCTION
In the following section, the main findings of the clinical and preclinical studies on cardiovascular effects of hyperoxia presented in this dissertation are summarized and discussed in a broader perspective.

Main findings
In chapter 2, we reviewed the literature on the effects of arterial hyperoxia during and after cardiac surgery. During these procedures, high oxygen concentrations are often routinely administered before, during and after cardiopulmonary bypass to be on the ‘safe side’ of oxygenation. The results of these studies show that hyperoxia decreases cardiovascular performance (i.e. reduced cardiac output) and may increase cardiac injury (increased Troponin-T and Creatine-Kinase) in cardiac surgery patients. No beneficial effects of hyperoxia on gas micro-emboli or postoperative infections were reported. However, these clinical studies have several methodological limitations. For one, none used a perioperative oxygenation protocol that included the intensive care unit (ICU), a vital period in the recovery of the patient. Second, the oxygenation targets in these studies were, compared to modern day practice, extremely high, even the ‘normoxic’ control groups.

In the study described in chapter 3, we considered these limitations and performed a randomized controlled trial in patients undergoing coronary artery bypass surgery. We compared near-physiological oxygen tensions to moderate hyperoxic targets during surgery and ICU admission. We found no differences between the two groups in terms of hemodynamic parameters, oxidative stress or myocardial injury. Lower oxygenation targets were not associated with hyperlactatemia, kidney dysfunction or hypoxic events, suggesting that near-physiological oxygenation targets can be applied safely during and after cardiac surgery.

In chapter 4, we investigated the dose-response relationship between hyperoxia, systemic hemodynamic variables, systemic oxygen delivery and the sublingual microcirculation in a group of healthy volunteers. The results suggest that hyperoxia does not alter systemic oxygen delivery but does cause a significant decrease in sublingual microcirculatory perfusion. The microcirculatory alterations became apparent above an arterial oxygen tension of 20 kPa.
Chapter 5 describes the results of a meta-analysis of studies addressing the effects of hyperoxia on systemic hemodynamic parameters and oxygen delivery in healthy volunteers and patients with cardiovascular disease. The meta-analysis shows that acute hyperoxia reduces cardiac output (by approximately 10%) and increases systemic vascular resistance (by approximately 12%) in healthy volunteers and non-hospitalized patients with compromised cardiovascular function. Patients with heart failure appear more susceptible to the cardio depressing effect of hyperoxia (15% decrease in cardiac output). In patients with sepsis, hyperoxia does not appear to affect systemic hemodynamics. In addition, we found no evidence that oxygen supplementation in the absence of hypoxemia increases systemic oxygen delivery.

In chapter 6, we developed an isolated artery model in attempt to identify the pathway(s) involved in hyperoxic vasoconstriction. Endothelium-dependent and -independent vasodilators and constrictor pathways were examined. We found that isolated murine first order arterioles of the gracilis muscle do not respond to hyperoxia with a change in diameter, suggesting that extravascular signals are important for hyperoxic vasoconstriction.

In chapter 7, we meta-analysed all in vivo and ex vivo animal studies addressing effects of acute hyperoxia on vascular tone. We found that the constrictor effect of hyperoxia was larger in vivo than ex vivo, further supporting the notion that the mechanisms responsible for hyperoxic vasoconstriction are not confined to the vessel wall. Hyperoxic vasoconstriction was most pronounced in the cremaster vasculature (muscle tissue) compared to intestines and skin. In addition, the magnitude of hyperoxic vasoconstriction increased as vessel diameter decreased and the greatest constriction was seen in vessels 15-25 μm in diameter.

**Hyperoxia and oxidative stress**

There is considerable evidence from both preclinical and clinical studies that hyperoxia is associated with production of reactive oxygen species (ROS). When the antioxidant capacity of tissue is overwhelmed, oxidative stress and tissue damage ensues. This is particularly undesirable in disease states where ROS play a central role, such as in patients with the systemic inflammatory response syndrome (e.g. patients after cardiac surgery, post-car-
Diastolic arrest or patients with sepsis) or patients with ischemia/reperfusion (e.g. myocardial infarction, cardiac surgery). Two studies in coronary artery bypass surgery patients showed that lowering oxygen concentrations during surgery lowered markers of oxidative stress and reduced myocardial damage\textsuperscript{15,16}. This is in contrast with our findings described in chapter 3, where we found no differences in oxidative stress between two clinically relevant oxygenation targets (P\textsubscript{a}O\textsubscript{2} range of 10-30 kPa). The most obvious difference of our investigation with previous studies is the magnitude of hyperoxia. In earlier investigations in CABG patients, P\textsubscript{a}O\textsubscript{2} levels of 53-73 kPa were induced during surgery\textsuperscript{15,16} and studies in patients\textsuperscript{6–9} or healthy volunteers\textsuperscript{7,10–14} applied an F\textsubscript{IO}2 of 100%. Similarly, preclinical studies also applied extreme oxygen tensions (PO\textsubscript{2} levels of approximately 95 kPa)\textsuperscript{1–5}. Our results described in chapter 3 suggest that ROS may not be a concern in more clinically relevant arterial oxygen tension ranges (P\textsubscript{a}O\textsubscript{2} levels up to 30kPa). However, it should be considered that the CABG patients included in our study were relatively healthy and therefore may have had adequate antioxidant defences. In critically ill or high-risk surgery patients with a more fulminant presence of oxidative stress (e.g. patients with sepsis), the tolerance level for hyperoxia may be lower.

**Hyperoxia and oxygen delivery**

The rationale behind abundant oxygen supplementation is to protect against cellular hypoxia or to boost tissue oxygen levels, with the assumption that “more oxygen is better”. However, as we have shown in chapter 4, no amount of supplemental oxygen enhances systemic oxygen delivery in healthy volunteers who are not hypoxemic. In addition, our meta-analysis in chapter 5 shows that hyperoxia does not enhance oxygen delivery in non-hypoxemic septic patients either. Oxygen delivery does not change because the small increase in arterial oxygen content caused by oxygen supplementation is negated by microvascular constriction and a reduction in cardiac output. On the other hand, we did not find evidence that the reduction in cardiac output actually decreases systemic oxygen delivery, at least in healthy volunteers (chapters 4 and 5). Surprisingly, there are only a few investigations on the effect of oxygen supplementation on oxygen delivery in patients. This should be further investigated because, as we have shown in chapter 5, cardiovascular effects of hyperoxia are not the same in all types of patients. For
instance, the hyperoxia-induced reduction in cardiac output in patients with heart failure is larger than in healthy volunteers or patients with coronary artery disease. In patients with heart failure, a disproportional decrease in cardiac output could lead to a reduction in overall oxygen delivery. In addition, even if systemic oxygen delivery remains unchanged, local tissue hypoxia may still occur due to substantial decreases in perfused microvascular vessel density.

Hyperoxia and perfusion

Hyperoxia may significantly reduce organ perfusion both centrally via a reduction in cardiac output, as well as locally through hyperoxic vasoconstriction. In healthy volunteers, hyperoxia can decrease cardiac output by 10% and reduce functional perfusion of the sublingual region by 15% (chapters 4 and 5). In animal studies, hyperoxia can reduce arteriolar diameter by approximately 20% which, following Poiseuille’s law, would roughly reduce blood flow by 60% (chapter 7). Interestingly, although the reported declines in perfusion are impressive, healthy individuals appear to be tolerant to these reductions. For instance, in chapter 4, we did not find increased blood lactate levels, which suggests that the reduction in perfusion does not substantially affect aerobic glycolysis. Also, neither we, nor any of the healthy volunteer studies included in the meta-analysis in chapter 5 reported the existence of adverse events related to breathing (pure) oxygen. This suggests that healthy tissue has either a considerable margin of tolerance for decreased flow, or has sufficient auto-regulatory mechanisms to prevent detrimental decreases in perfusion.

The results of chapters 6 and 7 suggest that extravascular tissue or circulating mediators are important for hyperoxic vasoconstriction to occur. Consequently, it is likely that when the restriction of perfusion results in (near) tissue hypoxia, tissue derived signals convert from constriction to dilatation. In the critically ill however, the control mechanisms for normal perfusion may fail. Disease states such as sepsis, post-cardiac arrest, cardiac surgery and acute heart failure are all associated with disturbed microcirculatory perfusion, even under normoxic conditions. Superimposed reductions in perfused vessel density due to hyperoxia have been observed in patients after CABG surgery and in a mixed group of ICU patients. If regional pathology
(e.g. vascular stenosis or localized microcirculatory alterations) already impairs perfusion under normoxic conditions, an additional vasoconstrictor signal could be detrimental for local oxygen and nutrient delivery, but also for disposal of metabolic waste. In pigs with coronary stenosis, hyperoxia increased myocardial ischemia. Similarly, one trial in patients with acute myocardial infarction who received oxygen supplementation developed a larger infarct area in comparison to patients receiving air\textsuperscript{27}. It is however unknown whether this was due to effects on perfusion or ROS production. Even if hyperoxia does not further impair perfusion due to vasoconstriction in the diseased tissue, the reducing effect of hyperoxia on cardiac output could lower the circulation of blood through already poorly perfused areas.

**Differential effects of hyperoxia**

Not every blood vessel, organ or patient is equally affected by hyperoxia. In chapter 7, we found that small arteries (15-25 μm) are more sensitive to hyperoxia than larger blood vessels. This could partially explain why we found that the arteries we studied in chapter 6, the isolated murine first order artery of the gracilis muscle, which is approximately 120μm in diameter, did not respond to hyperoxia. Furthermore, hyperoxic vasoconstriction was most pronounced in skeletal muscle, while the intestinal and skin vasculature showed reduced vasoconstriction in response to hyperoxia (chapter 7). Similar divergent reactions may occur in other organs (e.g. myocardial\textsuperscript{8,13} or cerebral vasculature\textsuperscript{28–30}).

In animal models of septic and haemorrhagic shock, hyperoxia has been shown to cause a redistribution of blood flow to vital organs such as the kidney, liver and intestines and, although marginal, this improved organ function\textsuperscript{31–33}. The redistribution may be caused by the reduced hyperoxic vasoconstriction in the intestinal area, causing it to receive a larger proportion of the cardiac output during hyperoxia. The reason for different response of the intestinal vasculature to hyperoxia is unclear but may be related to the high level of autoregulation of gut perfusion. For instance, inhibition of the nitric oxide pathway in the intestines only results in a transient reduction in diameter\textsuperscript{34}. Similarly, autoregulation of the intestinal vasculature quickly causes blood flow to restore to baseline after acute increases and decreases in arterial pressure\textsuperscript{35,36}. This indicates that several vasoactive systems cooperate
to maintain a certain level of perfusion. The mechanisms responsible for hyperoxic vasoconstriction may therefore not necessarily be absent in the intestines, but the decrease in diameter is quickly compensated for by other mechanisms. This differential effect of hyperoxia on organ perfusion may aid the supply of nutrients and immunologic mediators, as well as the removal of waste from organs.

Clinical studies are required because it is unclear whether this varying effect of hyperoxia on vascular tone is present in humans. In addition, it may not even be feasible in all patients. For instance, in chapter 5, we found that hyperoxia has no profound effects on systemic vascular resistance or cardiac output in septic patients, possibly due to the general vasoplegia seen in these patients. In a recent clinical trial with septic patients, hyperoxia (ventilation with an FIO2 of 1.0) did not induce sufficient vasoconstriction to reduce the need for vasopressor support.37 The study was however prematurely stopped due to increased mortality in the hyperoxia group. Conversely, in patients with coronary artery disease or heart failure, hyperoxia increased systemic vascular resistance substantially (15-25%), suggesting the presence of marked hyperoxic vasoconstriction. However, in these patients any redistribution of blood away from the heart may be detrimental. Taken together, the hemodynamic effects of hyperoxia depend on vessel type, organ and underlying pathology, which warrant further investigation into personalized oxygenation strategies.

**Magnitude of hyperoxia**

The extent of the hyperoxic exposure is an important factor to consider for patient care. Retrospective studies of cardiac arrest patients and the general ICU population suggest that the relation between hyperoxia and mortality is U-shaped. Increased mortality is found in the presence of hypoxia, but also in (extreme) hyperoxia. Interestingly however, the lowest mortality was found to be in the range of 15-20 kPa, which is mild/moderate hyperoxic, not extreme.38 In patients after cardiac arrest, moderate hyperoxia was even associated with improved organ function. In randomized controlled trials with patients after CABG surgery, extreme hyperoxia is associated with increased myocardial injury (chapter 2), but as we have shown in chapter 3, moderate hyperoxia is not. Similarly, the AVOID trial showed that oxygen administration
to patients with ST-elevated myocardial infarction leads to increased infarct size[^27], whereas the more recently performed DETO2X-AMI trial did not find such an effect[^39]. Although there were differences in patient selection and trial size, the administration of oxygen differed as well. In the AVOID trial, oxygen was supplemented at a rate of 8L/min via a closed facemask to patients presenting with a haemoglobin saturation of 94% or more. In the DETO2X-AMI trial, patients with a saturation of 90% or higher received oxygen at a lower rate of 6L/min via an open face mask. This difference in oxygen administration may have resulted in lower overall arterial oxygen tensions in the DETO2X-AMI trial and partly explain the contrasting results.

Evidently, adverse outcomes are associated with the degree of hypoxia. The retrospective nadir in mortality at moderate hyperoxic ranges (15-20 kPa) can be explained by a combination of our results described in chapter 3, chapter 4 and chapter 7. It seems that hyperoxia in the range of 15-20 kPa does not increase ROS induced tissue damage. Second, hyperoxic vasoconstriction occurs at any supraphysiological oxygen tension (chapter 7) and thus may cause a (slight) redistribution of blood flow to splanchnic organs while the hyperoxic vasoconstriction occurring in other areas are within the tissue perfusion margin of tolerance and cumulatively do not cause a significant change in cardiac output. In addition, moderate hyperoxia may provide a subtle buffer against desaturations due to acute increases in patient stress.

**Mechanisms of hyperoxic vasoconstriction**

The results of chapters 6 and 7 suggest that extravascular signals are important for hyperoxic vasoconstriction. However, the pathway(s) responsible for this increase in vascular tone has not yet been determined with certainty. The usual suspects include ROS production and reduced NO bioavailability, the modulation of arachidonic acid metabolism and increases in neurohormonal activity.

Most of the evidence for the involvement of ROS in hyperoxic vasoconstriction comes from human studies. Ascorbic Acid (vitamin C), predominantly a non-selective anti-oxidant molecule, prevented or restored hemodynamic changes imposed by hyperoxia when infused at sufficiently high doses[^7,9,13]. Orally administered anti-oxidants (beverages high in uric acid, vitamin
C tablets or a mixture of various anti-oxidants) gave similar results\textsuperscript{10,14,40,41}. However, similar to our results presented in \textit{chapter 3}, hyperoxia had no measurable effect on plasma F2-isoprostanes or ascorbic acid levels \textsuperscript{42,43}. This is not necessarily evidence against the involvement of ROS, because changes may still have occurred intracellularly. Conversely, less robust markers of oxidation (e.g. lipid hydroperoxides, thiobarbituric acid reactive substances) are increased by hyperoxia\textsuperscript{10,11,14,41,44}. Investigations regarding the involvement of the ROS superoxide (O$_2^-$) have given varying results. For instance, in \textit{in vivo} animal studies, superoxide dismutase does not prevent hyperoxic vasoconstriction, which argues against the involvement of superoxide\textsuperscript{45,46}. In \textit{ex vivo} studies on isolated arteries, superoxide was found to be involved indirectly; hyperoxic gassing led to generation of superoxide in the medium, rather than biologically in the isolated tissue\textsuperscript{5,47}. Taken together, hyperoxia appears to evoke vasoconstriction via a redox-sensitive pathway, which requires further examination.

Closely related to ROS exposure, hyperoxic vasoconstriction is postulated to be the consequence of reduced bioavailability of the vasodilator nitric oxide. Human studies have shown that hyperoxia reduced the concentration of plasma nitrite and nitrate, which indicates reduced production of NO\textsuperscript{11,44}. Local inhibition of the eNOS enzyme via iontophoresis of L-NMMA or L-NAME prevented hyperoxic vasoconstriction\textsuperscript{48}, or had no effect\textsuperscript{49}. Most \textit{in vivo} animal studies exclude the involvement of NO because the aforementioned blockers of eNOS had no effect on hyperoxia induced reductions in vessel diameter\textsuperscript{50–54}. Studies with isolated arteries show either no effect of hyperoxia on NO production\textsuperscript{55–57} or reduced production of NO\textsuperscript{58–60} under hyperoxic conditions.

A third pathway possibly affected by hyperoxia is the metabolism of arachidonic acid (AA). Endothelial cyclooxygenase (COX) can produce both vasoconstricting and vasodilating prostaglandins. In humans, the COX pathway has been sparsely investigated, but the COX-1 inhibitor aspirin prevented hyperoxia induced reductions in forearm blood flow, suggesting that aspirin and hyperoxia affect the same pathway\textsuperscript{40,61}. Surprisingly however, Ketolorac, a very potent and selective blocker of COX-1 had no effect, albeit was studied in just a single study\textsuperscript{48}. In the laboratory, multiple blockers of COX have been used with mixed results. \textit{In vivo}, indomethacin had no effect on hyperoxic
vasoconstriction\textsuperscript{45,54,62} and \textit{ex vivo}, overall, inhibiting prostaglandin synthesis only partially or transiently reduced hyperoxic vasoconstriction\textsuperscript{55,56,59,63–67}.

The Cytochrome P-450 ω-hydroxylase enzyme can convert AA to epoxyeicosatrienoic acids (EETs) with similar actions to prostaglandins. The most notable product is 20-HETE, which in most vasculatures acts as a vasoconstrictor\textsuperscript{68}. Several \textit{in vivo}\textsuperscript{54,69–74} and \textit{ex vivo}\textsuperscript{56,59} studies suggest that hyperoxia increases the production of 20-HETE. Interestingly, CYP450 is also highly expressed in small arterioles and extravascular tissue, such as skeletal muscle\textsuperscript{72}. In contrast, we found no indication of altered AA metabolism in our study on isolated first order arteries of the gracilis muscle (\textit{chapter 6}), which argues against the involvement of CYP450 or COX. However, vascular expression of CYP450 might be confined to arterioles smaller in diameter than the ones we used in our experiments. To our knowledge, the involvement of 20-HETE in hyperoxic vasoconstriction has not been investigated in humans.

In humans, hyperoxia has no effect on circulating concentrations of (nor)epinephrine\textsuperscript{11,75}, endothelin-1\textsuperscript{18,11} or serotonin\textsuperscript{76}. Neither did pharmacological blockade of alpha and beta adrenergic receptors change the hemodynamic response to hyperoxia\textsuperscript{77}. In \textit{chapter 6}, we also found that hyperoxia does not modulate the sensitivity of adrenergic receptors to noradrenalin. In healthy volunteers and patients with chronic heart failure, hyperoxia does not affect muscle sympathetic nerve activity\textsuperscript{78,79}. Taken together, the involvement of vasoactive hormones in hyperoxic vasoconstriction has not yet been shown.

The existence of varying and sometimes conflicting results from animal and human studies make the identification of pathway(s) involved in hyperoxic constriction difficult. This gamut of proposed mechanisms is likely the consequence of a wide variety in species (e.g., humans, rodents, ungulates), vascular beds (e.g., coronary, skin, muscle) and study methodologies (e.g., intravital microscopy, ultrasonography, \textit{ex vivo} vessel myography) used. In addition, in \textit{chapters 5} and \textit{7} we found that most studies lack power calculations, precise delivery/measurement of the hyperoxic intervention and quality control of the study preparation (e.g., verification of endothelial and smooth muscle integrity). In turn these deficits may have led to false positive and negative results on pathway involvement. Especially in studies were pathways are investigated via pharmacological blockade, conclusions on
their involvement in oxygen-mediated constriction is traditionally based on statistical significance. The latter is heavily influenced by group size and effect variation. Hence, pre-defined group sizes, along with sufficient variation control (e.g. quality control and oxygen dosing) are required to minimize the chance of false positives and negatives. New, high quality studies are therefore needed for a better understanding of hyperoxic vasoconstriction. As of now, 20-HETE seems a promising mediator of hyperoxic vasoconstriction.

Limitations
The studies presented in this dissertation do have some limitations. For one, the clinical studies (chapters 3 and 4) used relatively small sample sizes and specific study populations (i.e. low risk, male CABG surgery patients and young healthy volunteers). The results of these studies may be different in larger and more heterogeneous groups of patients/volunteers with different baseline characteristics. For instance, hyperoxia may have a different effect on oxidative stress if the patients under investigation have a worse anti-oxidative capacity at baseline. Furthermore, in the healthy volunteer study, we only evaluated the sublingual microcirculation. The changes described are likely to be different in other vascular beds.

The meta-analysis on the hemodynamic effects of acute hyperoxia (chapter 5) showed significant heterogeneity between studies related to heart rate, cardiac output, mean arterial pressure and oxygen delivery. The heterogeneity was partially caused by differences in the magnitude of hyperoxic exposure. However, we were unable to account for this heterogeneity because few studies actually measured arterial oxygenation targets. As such, although the subjects in the included studies were all exposed to pure oxygen, the true level of exposure may have been different due to biological (e.g. lung function) or methodological factors (e.g. oxygen leakage with the use of masks). Therefore, the true effect sizes may be different. Relatively few hemodynamic studies were performed in septic or CABG patients and studies in other groups of ICU patients (e.g. post-cardiac arrest) are completely lacking. In addition, there were no studies on the effect of hyperoxia on oxygen delivery in patients with coronary artery disease, heart failure or post-CABG patients, which is surprising, considering that these patients routinely receive supplemental oxygen.
In chapter 6, we studied the effect of hyperoxia on the vascular tone of isolated murine femoral arteries and first order arterioles feeding the gracilis muscle. The use of this arteriole in pressure myography setups is an established method to study pathways related to the control of vascular resistance and organ perfusion. We performed these studies without luminal flow, which may have influenced the response of the arterioles to hyperoxia. However, because we investigated the most prominent pathways involved in flow-induced vasoreactivity through agonist-induced activation of the endothelium, we do not think the lack of flow was a key aspect in our experiments. In addition, we only studied relatively large vessels (>120 μm in diameter) originating from the gracilis muscle. Experiments with smaller vessels, or vessels from another area (e.g. cremaster muscle) or species (e.g. rats) may give different results as described in chapter 7.

The quality of the studies included in the meta-analysis of in vivo and ex vivo animal studies was generally low (chapter 7). One of the main shortcomings of the studies was that oxygen tensions were not measured. Instead, oxygen concentrations were reported as being the level of exposure. Due to the absence of oxygen tensions, the comparability to arterial oxygen tensions is difficult. In addition, the majority of studies was performed on externalized tissue. Taken together, it is unclear if the magnitude of hyperoxic constriction seen in these studies reflect the effects in intact animals or humans.

Finally, a limitation that applies to all studies presented in this dissertation, is that the cerebral and lung vasculature were not considered. The brain was excluded because it is known to have a highly complex system of auto-regulation which differs from other vascular beds. Similarly, the lung was excluded because it has known to respond differently to oxygen, most notably is the presence of hypoxic constriction in the lung as opposed to hypoxic dilation in other organs. The brain and lung were excluded to increase the focus of our own investigations.

**Future investigations**

Studies investigating the effect of hyperoxia on oxygen delivery in cardiac patients are currently lacking. Considering that the hemodynamic effects of hyperoxia are most pronounced in heart failure patients and the decline in cardiac output may decrease overall oxygen delivery, it would be very valu-
able to see if this is indeed the case. Likewise, (more) oxygen delivery studies should be performed in common ICU populations, for instance in patients after cardiac arrest and patients with sepsis because they are one of the most frequent type of ICU patients that receive mechanical ventilation.

In addition to overall oxygen delivery, organ specific studies targeting the liver, kidney and intestines in humans and animals are warranted as well. On the one hand to investigate whether hyperoxia is able to impair blood flow to these organs, on the other to detect if the differential vasoconstrictor effect of hyperoxia indeed redirects blood flow to certain critical organs in patients. If indeed perfusion changes are detected, it would additionally be important to assess if they result in functional changes; for instance, whether hyperoxia affects the ability of the liver to eliminate indocyanine green.

For all studies, we propose to establish several intermediate arterial oxygen tensions (e.g. 11, 20, 40 and 60 kPa) to facilitate the translation of studies to clinical practice. Because oxygenation protocols can differ substantially between hospitals and even departments, investigating several oxygen dosages will help to judge whether the observed effects are relevant for current practice.

Ultimately, to truly test the safety and harm or benefit of hyperoxia, more prospective randomized controlled trials with clinically relevant endpoints (e.g. mortality, neurological outcomes, organ function) must be performed in populations who routinely receive oxygen supplementation such as patients after cardiac arrest, patients with sepsis, patients undergoing surgery and patients with heart failure. A returning difficulty in these type of studies is monitoring arterial oxygen tensions to ensure protocol adherence. Currently, frequent arterial blood gas sampling is performed to do so, which is hardly an ideal solution for everyday practice due to the necessity of an arterial line and the additional sampling burden for patients and medical personnel. Pulse oximetry is insufficient to monitor the magnitude of arterial hyperoxia because it only measures haemoglobin saturation, which at normoxic ranges is already saturated for 96-98%. However, a new type of pulse oximeter, which measures the ‘oxygen reserve index’ (ORI), is currently under development. The ORI is advocated to reflect oxygenation in the moderate hyperoxic range (P<sub>O</sub><sub>2</sub> of 13-27 kPa)\(^8\). Because the device is identical to regular pulse oximeters in use, it may be a solution for better oxygen titration in
the ambulatory setting and reduce the frequency of blood gas sampling for monitoring arterial hyperoxia.

**Hyperoxia and clinical practice**

Results of prospective, randomized controlled trials investigating the effect of hyperoxia on clinical outcomes are starting to emerge. Although each study has its methodological limitations, most trials report a negative association between hyperoxia and mortality or indices of organ injury. In a mixed population of ICU patients or patients with sepsis, hyperoxic oxygenation targets increase the risk of mortality. In patients with myocardial ischemia, oxygen supplementation has the potential to increase infarct size, but does not appear to affect mortality. In addition, none of these studies reported beneficial effects of hyperoxygenation. The postulated antimicrobial application of hyperoxia is questionable due to the increased mortality seen in patients with sepsis, and a lack of effect on surgical site infections after abdominal surgery. Taken together, these recent developments challenge the rationale behind the use and safety of hyperoxia.

The work in this dissertation adds to this perspective from a clinical and physiological point of view. Contrary to popular belief, hyperoxia does not increase systemic oxygen delivery at any hyperoxic arterial oxygen tension. Instead, significant vasoconstriction in the microcirculation, combined with a central reduction in cardiac output, has the potential to cause or exacerbate tissue hypoxia. Furthermore, using lower oxygenation targets during CABG surgery and ICU admission appears safe. On the other hand, the benefit of hyperoxia appears limited. Possible beneficial effects of moderate hyperoxia on the redistribution of blood flow to critical organs require further investigation. For now, being on “the safe side” in terms of oxygenation, we propose to strive for normoxia rather than hyperoxia, considering that hyperoxia does not improve oxygen delivery but rather brings risk of significant reductions in perfusion.
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